UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606** **HON. ROBERT B. KUGLER** **HON. JOEL SCHNEIDER** **CIVIL NO. 15-2606 (RBK)(JS)**
THIS DOCUMENT RELATES TO ALL CASES	

PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE TESTIMONY OF PLAINTIFFS' EXPERT SUSAN HUTFLESS, Ph.D.

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Plaintiffs hereby file their instant Memorandum of Law in Opposition to Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Susan Hutfless, Ph.D.

PRELIMINARY STATEMENT

The science and medicine establishing that olmesartan medoxomil causes sprue-like enteropathy, olmesartan-associated enteropathy, or olmesartan-induced enteropathy (hereinafter referred to as SLE, OAE, or OIE interchangeably) is not merely compelling, but is well-established. Both the extensive body of published peer-reviewed medical literature and the general acceptance of this causal relationship by clinicians around the world refute any assertion that there somehow remains an open question.

This is not a case where law leads science. Rather, the robust causation evidence has caused a definitive shift in clinical practice within the gastroenterological and larger medical community. In fact, practitioners are now directed to consider olmesartan as an underlying risk factor for development of gastrointestinal events. The current state of medical knowledge evidencing the relationship between olmesartan and SLE include over two hundred peer-reviewed case reports and case series, epidemiological evidence showing an over 10 times risk for becoming hospitalized for malabsorption or celiac disease while on olmesartan

for more than two years, as well as several publications that discuss the histology of what is occurring at the cellular level in the intestinal tract.

Not only are Dr. Susan Hutfless's methodologies valid and generally accepted, but her conclusions are sound and represent established medical opinion. *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 594 (1993) (holding "widespread acceptance can be an important factor in ruling particular evidence admissible"). Indeed, there is no dispute that Dr. Hutfless used the well-accepted Bradford Hill criteria as her methodology, which even the defense experts agree she applied correctly. Unfortunately, Daiichi seems compelled to file *Daubert* motions in every case involving causation, even when the evidence is overwhelming and voluminous, as here.

Just as Defendants (hereinafter referred to collectively as "Daiichi") are disregarding the massive, applicable body of medical and scientific evidence, Daiichi asserts very little case law for its claim that Dr. Hutfless' opinions are unreliable, and instead attempts to mischaracterize her testimony or the medical evidence supporting her opinions, as well as falsely accuse her of not considering specific studies which the Defendants believe support their position. However, Dr. Hutfless's opinion takes into account *all* of the scientific studies, both positive and negative, to reach her opinions in this case. This is a reliable methodology and

any attacks leveled at her conclusions are merely towards the weight of the evidence. Therefore, Daiichi's motion should be denied in its entirety.

FACTUAL BACKGROUND

A. There Is No Dispute That Dr. Hutfless Is Exceptionally Qualified To Render Opinions on Causation.

Dr. Susan Hutfless is a Ph.D. epidemiologist specializing in examining the causes and treatments of gastrointestinal disorders, including assessing harms of medications. (*See* Hutfless *Curriculum Vitae*, Sutton Cert.[1], Ex. 1; Hutfless Dep. Tr., Ex. 2, at 73:21-74:4; 76:11-77:9.) Dr. Hutfless is the Director of the Gastrointestinal Epidemiology Research Center and a member of the Center for Drug Safety & Effectiveness at Johns Hopkins University, as well as an Assistant Professor of Medicine in the Gastroenterology Division of Johns Hopkins University. (*Id.*) As Director of the Gastroenterology Epidemiology Research Center, Dr. Hutfless performs epidemiology related to gastrointestinal disorders within the gastroenterology division of Johns Hopkins University. (Hutfless Dep. Tr., Ex. 2, at 80:20-81:20.) With over 10 years of experience conducting epidemiologic research specifically related to gastroenterology, she is nationally and internationally known for examining the epidemiology of gastrointestinal disorders. (*Id.* at 80:20-81:20.) A large part of Dr. Hutfless' work relates to drug safety

[1] Hereinafter each exhibit is referenced in the Certification of Tara D. Sutton, Esq.

research. (*Id.* at 72:20-73:13.) Dr. Hutfless also serves as a faculty member with the Evidence-Based Practice Center, a healthcare research and quality, funded center that performs systematic reviews. (*Id.* at 73:16 – 75:3.)

B. There Is No Dispute That The Bradford Hill Criteria Used By Dr. Hutfless Is A Well-Accepted And Reliable Scientific Methodology.

When Dr. Hutfless became involved in this litigation, she approached the question of causation by undertaking a critical review of the relevant medical literature and studies. (*See* Hutfless Report, Ex. 1, at 16). Dr. Hutfless details the methodology that she employed for selecting and weighing the numerous sources of evidence, which included the well-accepted and scientifically reliable Bradford Hill criteria. (*See* "Summary Table," in Hutfless Report, Ex. 1, at 6-10; Hutfless Dep. Tr., Ex. 2, at 409:5-21.)

Dr. Hutfless conducted an independent search that spanned all levels of evidence, including 213 published case reports, non-randomized studies of the specific adverse events, and randomized clinical trials. (*See* Hutfless Report, Ex. 1, at 20-21; Hutfless Updated Table 10, Ex. 3; Hutfless Dep. Tr., Ex. 2, at 49:16-21.) None of the evidence was "ignored" or "disregarded," and certainly not as to the four retrospective studies Daiichi claims. (*See* Defs. Br. at 3-4, ECF Dkt No. 1069.) Her systematic review involved applying the same Johns Hopkins Evidence-Based Practice Center methodology utilized by her university and consistent with the

AHRQ EPC Methods Guide and Cochrane Handbook, both known for producing high quality systematic reviews. (*See* Hutfless Report, Ex. 1, at 11; Hutfless Dep. Tr., Ex. 2, at 5:15-22.) This involves conducting a double review of the initial data. (*See* Hutfless Dep. Tr., Ex. 2, at 5:15-22; 20:23-22:14.)

Using this framework, Dr. Hutfless systematically reviewed three sources of information collectively (*see* Hutfless Report, Ex. 1, at 16): (1) a highly specific subset of MedWatch cases reported by Daiichi to the FDA, including only serious rechallenge cases of celiac, vomiting or diarrhea, identified by gastroenterologist Daniel Leffler, M.D., as relevant to his diagnosis of OIE (*id.* at 17-18); (2) a review of the association between olmesartan and the adverse events reported to the FDA Adverse Event Reporting System (FAERS)[2] (*id.* at 19-20); and (3) systematic and independent review of the published literature (*id.* at 20-35).

Based on all of this evidence, Dr. Hutfless concludes with a reasonable degree of scientific certainty, that there is sufficient evidence to establish a causal relationship between olmesartan and enteropathy. (*See id.*; Hutfless Dep. Tr., Ex. 2, 162:22-163:9). Moreover, "[h]ad the manufacturer investigated cases with

[2] Defendants do not dispute that Dr. Hutfless FAERS analysis used a proper methodology and therefore is reliable evidence to support her general causation opinion. Nor could they since Dr. Hutfless's analysis is fully consistent with the FDA's own FAERS analysis which led to olmesartan's label change and Drug Safety Communication. (*See* July 3, 2013 Drug Safety Communication to Healthcare Providers and Patients, Ex. 4.)

symptoms of celiac disease from their own trials in response to the positive rechallenge case reports and signals from FAERS in 2006, a causal association could have been detected and established at that time." (*Id.*).

LEGAL ARGUMENT

A. *Daubert* As Applied in the Third Circuit.

The admissibility of expert testimony is determined pursuant to Rule 702, which incorporates the *Daubert* standard. "Rule 702 has a liberal policy of admissibility." *Geiss v. Target Corp.*, 2013 WL 4675377 at *4 (D.N.J. 2013) (citing *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008)) (other citations omitted). The Third Circuit, "made clear in *Paoli II,* an expert's level of expertise may affect the reliability of the expert's opinion." *Elcock v. K-Mart Corp.*, 233 F.3d 734, 746 (3rd Cir. 2000) (quoting *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 741 (3d Cir. 1994) ("*Paoli II*")). Dr. Hutfless's extensive qualifications, including publication of peer reviewed literature on this subject, should therefore bear upon the reliability inquiry. *See Elcock*, 233 F.3d at 746; *Paoli II*, 35 F.3d at 741. Moreover, the reliability requirement should not be applied too strictly, but rather "[h]elpfulness to the trier of fact remains the ultimate touchstone of admissibility." *Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 783 (3d Cir. 1996).

Daubert requires that an expert, whether basing his opinions upon studies or personal experience, "employs in the courtroom the same level of intellectual rigor

that characterizes the practice of an expert in the relevant field." *Elcock*, 233 F.3d at 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)). Dr. Hutfless applied the methods and knowledge she uses within the gastroenterology department, as an epidemiologist at Johns Hopkins University, and has published in the peer-reviewed medical literature, clearly satisfying these standards. (Hutfless Dep. Tr., Ex. 1, at 80:20-81:20).

In fact, the Defendants agree that the method employed by Dr. Hutfless is a reliable and scientific methodology. (*See* Defs. Br. at 1) (stating the "well-established Bradford Hill factors to arrive at an opinion on general causation . . . would be a sound methodology if appropriately applied"). Daiichi's epidemiologist, Richard Hansen, agrees that Dr. Hutfless applied the correct methods and systematic review, and simply arrived at different conclusions. (Hansen Dep. Tr., Ex. 5, at 55:15 - 56:8; *see also* 283:12-284:2.) Indeed, Dr. Hansen, did not conduct a full literature review, relying instead on Dr. Hutfless' comprehensive review. (*See* Hansen Dep. Tr., Ex. 5, at 190:17-23.) Thus, the only question raised by Daiichi is noting medical literature which they claim disagree with her conclusion (even though it does not) and likewise attacking her conclusion on when a causal association was established. This is not a permissible attack under *Daubert*. The focus of the reliability inquiry is on the expert's principles and methodology, not on her conclusions. *Glynn v. Merck Sharp & Dohme Corp.*, 2013 WL 1558690, at *2 (D.N.J. April 10, 2013),

citing *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594-95 (1993). Daiichi's allegations only go to the weight of Dr. Hutfless's testimony, not its admissibility. *See In re Xarelto (Rivaroxaban) Prod. Liab. Litig.*, Case No. 2:14-MD-02592, Doc 6198, 2017 WL 1352860, at *4, attached as Ex. 6 (E.D. La. April 13, 2017) (denying all *Daubert* motions against plaintiff's experts, finding that "Defendants' arguments go to the witness's conclusions, not [their] methodology or qualifications").

B. Dr. Hutfless's Definition Of SLE Is Sound.

Daiichi's claim that Dr. Hutfless "cannot define sprue-like enteropathy" is belied by Daiichi's very next sentence explaining that Dr. Hutfless does in fact define SLE as a constellation of gastrointestinal symptoms, fully consistent with all of the Plaintiffs' experts and the medical literature. (Defs. Br. at 12.)

In her report, Dr. Hutfless's report examines "if olmesartan is a component cause of symptoms with what is now often referred to as olmesartan-induced enteropathy." (*See* Hutfless Report, Ex. 1, at 15.) Because the OIE terminology came into use after the acceptance of the association (and thus a search for OIE would not be helpful), Dr. Hutfless examined conditions and symptoms associated with enteropathy, including celiac disease, diarrhea, weight loss, dehydration and vomiting. (*Id.*) These symptoms were identified in consultation with Dr. Leffler, a

gastroenterologist with clinical expertise in celiac disease and treating olmesartan enteropathy, as well as in the medical literature. (*Id.*)

In her deposition, Dr. Hutfless was repeatedly asked to define SLE. (*See e.g.* Dep. Tr., Ex. 2, at 169:16-170:21; 174:3-10; 174:11-175:5; 175:7-176:2; 179:6-181:6.) Dr. Hutfless explained each time that her definition was formed in consultation with Dr. Daniel Leffler, a gastroenterologist, and a review of the medical literature:

> [S]ymptoms consistent with olmesartan-induced enteropathy include olmesartan-induced enteropathy itself, spruelike enteropathy, **enteropathy, malabsorption, diarrhea, weight loss, dehydration, vomiting, abdominal pain, and of course misdiagnosis with celiac disease or celiac-like symptoms**.

(*Id.* at 180:12-181:6) (emphasis added). Dr. Hutfless's definition is consistent with the incredibly large amount of medical literature describing SLE and the symptoms associated with it.[3] Moreover, Dr. Hutfless did not blindly adopt Dr. Leffler's

[3] *See e.g.* Choi EY, McKenna BJ. Olmesartan-Associated Enteropathy: A Review of Clinical and Histologic Findings. Arch Pathol Lab Med 2015;139:1242-7, attached as Ex. 7 (stating "[m]ost patients with OAE present with chronic nonbloody diarrhea and weight loss. Other commonly reported symptoms are fatigue, nausea, vomiting, abdominal pain, and bloating"); Fiorucci, Puxeddu, et al. *Severe spruelike enteropathy due to olmesartan*. Rev Esp Enferm Dig. 2014 Feb;106(2):142-4, attached as Ex. 8 (symptoms of SLE patient include diarrhea, weight loss, dehydration, low potassium, low magnesium, low albumin, low total protein, low B12, hospitalization); Marietta, Cartee, et al. *Drug-Induced Enteropathy*. Dig Dis. 2015;33(2):215-20, attached as Ex. 9 (symptoms of OAE include diarrhea, abdominal pain, weight loss, hospitalized several times for dehydration, acute kidney injury and hypotension); Ianiro G, Bibbo S, Montalto M, Ricci R, Gasbarrini A and Cammarota G. *Systematic review: sprue-like enteropathy associated with*

causation opinions, as the Defendants portray in their brief. (Defs. Br. at 12-13.) Rather, Dr. Hutfless worked collaboratively with a clinician to understand the symptoms of OAE, and then independently came to her own opinions on causation. (Hutfless Dep. Tr., Ex 2, at 97:19-99:9.) In fact, Dr. Hutfless never even had a conversation with Dr. Leffler regarding his opinions on causation. (*Id.*)

Daiichi similarly identified the symptoms of "olmesartan induced sprue-like enteropathy" in deposition testimony referring to internal documents, as "nausea, vomiting, diarrhea, and weight loss, some or all of these symptoms." (Dep. Tr. Tina Ho, Ex. 12, 451:18-453:15). Additionally, Defendants' own epidemiologist expert, Dr. Hansen, also consulted with a gastroenterologist for signs and symptoms consistent with SLE. (*See* Hansen Report, Ex. 13, at 6) (explaining that a "gastroenterologist with expertise in small bowel . . . reviewed the scientific literature on 'spruelike enteropathy' and recommended the following list of preferred terms to capture relevant terminology"); *see also* Hutfless Dep. Tr., Ex. 2, 171:7-21.) Tellingly, Daiichi does not cite to any of its own witness's testimony,

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olmesartan. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23, Ex. 10 (noting almost all of the 54 patients diagnosed with OAE presented with diarrhea and weight loss); Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, Wu TT, Rubio-Tapia A and Murray JA. *Immunopathogenesis of olmesartan-associated enteropathy*. Aliment Pharmacol Ther. 2015 Dec;42(11):1303-14, Ex. 11 ("olmesartan-associated enteropathy shares many features with coeliac disease, including **symptoms** and immunopathogenic pathways") (emphasis added)).

documents, or the medical literature when "defining" the symptoms of SLE in its motion. (*See* Defs. Br. at 7.)

Daiichi also argues without citing any legal authority that Dr. Hutfless is not permitted to rely on clinicians or medical literature for her definition of SLE. (*See* Defs. Br. at 12-13.) But the law is very clear that experts are allowed to rely on both. *See e.g. Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 781-82 (3d Cir. 1996) (treating physician properly relied on a pathology report to confirm diagnosis); *In re Jacoby Airplane Crash Litig.*, No. 99-6073 (HAA), 2007 U.S. Dist. LEXIS 69291, at *52 (D.N.J. Sep. 18, 2007) ("[I]t is common in technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert knowledge not possessed by the first expert; and it is apparent from the wording of Rule 703 that there is no general requirement that the other expert testify as well."); *Schneck v. IBM*, Civ. No. 92-4370 (GEB), 1996 U.S. Dist. LEXIS 17486, at *5 (D.N.J. June 25, 1996) (the epidemiologist "had good grounds for relying on the studies she used in formulating her general causation conclusion"); *Keller v. Feasterville Family Health Care Ctr.*, 557 F. Supp. 2d 671, 681 (E.D. Pa. 2008) ("no support exists in the text or history of the Federal Rules of Evidence, or case law to limit an expert from reviewing and referring to the opinions of other experts. To the contrary, Rule 703 authorizes an expert to use any data reasonably relied upon by experts in the field."); *Carnegie Mellon Univ. v. Marvell Tech. Grp.*, Ltd., 286

F.R.D. 266, 271 (W.D. Pa. 2012) (providing that "it is well-settled that one expert may rely upon another expert's opinion in formulating his[/her] own"). Given that Dr. Hutfless's definition of SLE is consistent with the medical literature, the plaintiff and defense experts, the FDA, and the Daiichi's own internal definitions for MedWatch coding purposes, Daiichi's argument that she could not define SLE is without merit.

C. Dr. Hutfless Generates Reliable Opinions on Causality Based on Multiple Lines of Reliable Evidence.

As recognized in the *Reference Manual on Scientific Evidence*, the Bradford Hill methodology is widely accepted in the field as a valid methodology for assessing causality.[4] Federal Judicial Center, Reference Guide on Epidemiology (3d ed. 2011), 599-606. Ex. 14. The Bradford Hill considerations are used to determine general causation and to identify whether exposure is the cause of the disease by considering the following nine elements: temporal relationship; strength of the association; dose-response relationship; replication of results; biological plausibility; alternative explanations; effect of ceasing exposure; specificity; and consistency with other relevant knowledge. *Id.* at 600-606. In complex tort actions, courts regularly hold that the Bradford Hill criteria are a sound and accepted

[4] The FDA also advocates use of the Bradford Hill considerations for interpreting pharmacoepidemiologic evidence. *Industry Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, at 18, 3/22/2005, Ex. 18.

methodology for evaluating general causation. *See, e.g., In re Avandia Marketing, Sales Practices and Products Liability Litigation*, 2011 WL 13576, at *3 (E.D. Pa. Jan. 4, 2011); *Gannon v. U.S.*, 292 Fed. Appx. 170, 173 (3d Cir. Sept. 8, 2008) (Bradford Hill criteria are "widely used in the scientific community to assess general causation"); *Magistrini v. One Hour Martinizing Dry Cleaner*, 180 F. Supp. 2d 584, 592-93 (D.N.J. 2002) (in determining whether a causal relationship exits, scientists apply various factors commonly referred to as the "Hill criteria"). In *Glynn v. Merck Sharp & Dohme Corp.*, the motion to preclude plaintiffs' expert on general causation was denied because, as here, the expert considered the Bradford Hill factors, and the criticisms went to the weight, not admissibility of the testimony, concluding, "Defendant is free to address these issues on cross-examination…" 2013 WL 1558690, at *4 (citing *Magistrini*, 180 F. Supp. 2d 584, 593 n. 9 (D.N.J. 2002)).

Daiichi acknowledges Dr. Hutfless's vast experience and knowledge with applying Bradford Hill criteria to gastrointestinal disorders, and that she in fact considered and applied all of these factors, leaving Daiichi to only argue that she "inconsistently" applied the factors. (*See* Defs. Br. at 28, 31). The focus of the reliability inquiry is on the expert's principles and methodology, not on her conclusions. *Glynn v. Merck Sharp & Dohme Corp.*, 2013 WL 1558690, at *2.

1. Dr. Hutfless Conducted An Independent Systematic Review That Included Reviewing *All* Medical Literature.

Dr. Hutfless did not "cherry-pick" epidemiological data as Daiichi claims. (*See* Defs. Br. at 4.) Rather, Dr. Hutfless conducted a full literature review, a methodology that is reliable under *Daubert*. *See, e.g. In re Neurontin*, 612 F. Supp. 2d 116, 161 (D. Mass. 2009); *Ferguson v. Lear Siegler Servs.*, 2012 U.S. Dist. LEXIS 42342 (M.D. Ala. Mar. 28, 2012) (reliance on peer-reviewed articles and experimentation conducted by others is reliable); *Tressler v. BNSF Ry. Co.*, 2012 U.S. Dist. LEXIS 11837 (E.D. Wash. Feb. 1, 2012)(medical and scientific literature review and evaluation of available epidemiological data is reliable methodology); *Facciponte v. Briggs & Stratton Corp.*, 2011 U.S. Dist. LEXIS 119293 (M.D. Pa. Oct. 17, 2011) (extensive review of the existing literature created a sufficiently reliable methodology); *In re Avandia Mktg.*, 2011 U.S. Dist. LEXIS 479, 26-27 (E.D. Pa. Jan. 3, 2011) (the review of peer-reviewed, published studies and data is reliable scientific methodology).

Moreover, there is absolutely no requirement – scientifically or based on the case law – that *every* Bradford Hill criteria must be satisfied. There is no "checklist" as the Defendants imply in their brief, but rather Bradford Hill is a framework for examining evidence in its totality. *Magistrini*, 180 F. Supp. 2d. at 593 n. 9; *see also* Hutfless Dep. Tr., Ex. 2, at 385:2-12. "One or more of the factors may be absent

even where a causal relationship exists and…no factor is a sine qua non of causation." *Glynn*, 2013 WL 1558690, at *3.

Defendants level no serious attacks on Dr. Hutfless's application of the Bradford Hill criteria, but rather only take issue with how she applied three of the nine factors: strength of association, biological plausibility and specificity (*see* Defs. Br. at 28-40.) While not every Bradford Hill criteria must be satisfied, Dr. Hutfless properly applied these three criteria to each line of evidence, i.e., the medical literature, the clinical trials, her FAERS analysis, as well as a highly specific set of serious rechallenge MedWatch cases written by Daiichi. (*see* Hutfless Report, Ex. 1, at 7-10).

2. Dr. Hutfless Properly Assessed the "Strength of Association."

Important to the causation analysis are the studies of olmesartan which measure the relative risk of suffering SLE after olmesartan exposure, and the magnitude of this risk. *See generally Reference Manual of Scientific Evidence*, at 549-624 ("The higher the relative risk, the stronger the association and the lower the chance that the effect is spurious"). For olmesartan and SLE, the highest calculated statistically significant relative risk is 10.65 — even higher than the relative risk

reported for the causal relationship between smoking and lung cancer (10).[5] According to the *Reference Manual*, a relative risk of 10 "is so high that it is extremely difficult to imagine any bias or confounding factor that might account for it." *Id.* at 602.

Daiichi's argument as to this factor is limited to claiming that Dr. Hutfless "ignored" four of the five retrospective studies, which Daiichi believes "failed to find an association between olmesartan and sprue-like enteropathy." (*See* Defs. Br. at 4.) This claim is easily dispelled by a simple review of Dr. Hutfless's report where she specifically addressed the strengths and weaknesses of each of these studies. (*See* Hutfless Report, Ex. 1, at 24-28). Indeed, Dr. Hutfless diligently reviewed all of the studies and data involving olmesartan, including their designs and limitations. (*See* Hufless Report, Ex. 1, at 21, 24-28.)

Specifically, Dr. Hutfless found that of the five retrospective studies reporting on gastrointestinal adverse events, only the *Basson* study specifically aimed to study whether olmesartan causes enteropathy, while controlling for confounders (*see* Report at 28.) Using insurance claims data from 2007 to 2012, the study compared OIE events in patients taking olmesartan versus other ARBs or ACE inhibitor (*see*

[5] Basson, Mezzarobba, et al. *Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study*. Gut. 2015 Aug 6. pii: gutjnl-2015-409690, at Ex. 16.

Report at 28.) The *Basson* study found that the rate of hospitalization for malabsorption and celiac disease was 3.66 times greater for 1-2 years of olmesartan use, and 10.65 times greater with 2 or more years of olmesartan use compared with ACE inhibitor use. *See* Ex. 16. Both findings were statistically significant. Dr. Hutfless found "it is rare to encounter this magnitude of a statistically significant finding." (*See* Hutfless Report, Ex. 1, at 28.) Dr. Hutfless' high opinion of the *Basson* study is consistent with the peer-reviewed and published literature, which considers the study "well-conducted" and "puts to bed any controversy surrounding the association between the ARB olmesartan and severe intestinal enteropathy pathologically resembling celiac disease." Talley, N. *Use of Olmesartan for ≥ 1 year was associated with hospitalization for intestinal malabsorption*, Ann Intern Med, 2015 Dec 15:163(12):JC13 (providing the clinical impact rating of the *Basson* study 7/7 stars for GI) at Ex. 17. Contrary to Daiichi's claim, "selection bias" and "confounding factors" were carefully considered. *Id.*

Dr. Hutfless also reviewed the Mini-Sentinel report by the FDA and concluded that the study is evidence of a causal relationship between olmesartan and SLE. (*See* Dep. Tr. 338:21-339:11). In fact, the Mini-Sentinel study was one of the sources of information used to inform the label change and FDA Drug Safety Communication, which concluded that olmesartan *can cause* SLE. (*See* FDA Tracked Safety Issue (TSI) Memorandum, Ex. 18; 7/3/2013 Drug Safety

Communication, at Ex. 4). Daiichi's expert calculated that Mini-Sentinel showed 2.72 times increased risk of a celiac disease diagnosis, versus other ARBs after two years of use. (*See* Ex. 13 at 9). Thus, the Mini-Sentinel[6] findings are consistent with Dr. Hutfless's causal opinion.

Nor did Dr. Hutfless ignore the *Greywoode*, *Lagana*[7], or *Padwal* studies[8]. (*See* Hutfless Report, Ex. 1, at 24-26.) First, she noted with *Greywoode* that only

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[6] Interestingly, Defendants attack the *Basson* study for using ICD codes even though the Mini-Sentinel study also used the same ICD code (celiac disease) and thus endpoint to analyze the relative estimate for OIE (Mini-Sentinel Study, Ex. 19; *see also* Dep. Tr. 295:10-17; 297:7-14). Indeed, the *Basson* study was more specific by examining patients with celiac disease *and* hospitalization and adjusts for confounders (Dep.. Tr. 300:2-3; 315:13-21.) The Mini-Sentinel study is also limited by a smaller subset of population (*id.* at 316:19-317:4.) Moreover, even if the studies conflicted with each other (which they do not), the mere fact that there is a conflict among studies does not control admissibility; rather it is the function of the factfinder. *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 285 (E.D.N.Y. 2007).

[7] Somewhat puzzling, the *Lagana* and *Greywoode* articles invoked by Daiichi are authored by the Plaintiffs' experts, Dr. Benjamin Lebwohl and Dr. Stephen Lagana, who are both opining that olmesartan causes SLE. Any attempt by the Defendants to claim these studies support the defense experts' conclusions or somehow negate the plaintiff experts' opinions, is without merit. Dr. Lebwohl explained that these studies were underpowered to evaluate the causal association of olmesartan and SLE and did not change his opinion. (*See* Lebwohl Dep. Tr., Ex. 20, at 145:3-147:5; 238:15-240:17; Lebwohl Expert Report, Ex. 21, at 15-17.) This is also consistent with the peer-reviewed medical literature. *See e.g.*, Choi at 43, at Ex. 7 (noting that the Lagana study "was limited by small sample size and lack of follow-up information regarding patient outcomes").

[8] Greywoode R, et al. *Olmesartan, other antihypertensives, and chronic diarrhea among patients undergoing endoscopic procedures: a case-control study*, at Ex. 22. Mayo Clin Proc 2014;89:1239-43; Lagana, SM, et al. *Sprue-like histology in*

105 total users of olmesartan were identified, and – like Daiichi's expert Dr. Risch found – the study failed to account for confounding[9] by comorbidities or other medications, and therefore the study did not contribute to the evidence of causal association. (*Id.*; Risch Dep. Tr., Ex. 25, at 307:45-308:13.) Likewise, for the *Lagana* study, Dr. Hutfless noted that the previous *Greywoode* study was modified to identify 20 patients undergoing endoscopy who had an indication for abdominal pain and documented olmesartan use, and then compared to 20 individuals with use of another ARB. (Hutfless Report, Ex. 1, at 25). Villous atrophy was present in 25% of evaluated olmesartan users compared with 6-11% of the other groups. (*Id.*). Dr. Hutfless concludes that "[d]ue to the design limitations (primarily no adjustment for confounding), this study does not contribute to the evidence of the causal relationship between olmesartan and olmesartan-induced enteropathy." (*Id.*). After reviewing *Padwal*, Dr. Hutfless determined the study lacked specificity as to the symptoms of OIE and lacked an examination of celiac disease, malabsorption, or composite symptoms associated with enteropathy. (*Id.*) Of note, Daiichi's epidemiologist, Dr. Risch, also found *Padwal* of little value, testifying that the

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patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers. J Clin Pathol. 2015 Jan;68(1):29-32. Epub 2014 Oct 23, Ex. 23; Padwal, R., et al. *Comparative effectiveness of olmesartan and other angiotensin blockers in diabetes mellitis: retrospective cohort study*. Hypertension. 2014:May;63(5):977-83, attached as Ex. 24.

background rate of gastrointestinal events may have masked the effect of olmesartan and also concluding that the events measured were not "specific enough" to detect olmesartan enteropathy in the population studied. (Risch Dep. Tr., Ex. 25, at 313:8-14; 318:2-22.)

Daiichi's epidemiologist reviewed Dr. Hutfless's analysis of clinical trial data and concluded it "was correct that there wasn't enough in them to bear – to worry about." (Risch Dep. Tr., Ex. 25 at 122:23-123:5.) Contrary to Daiichi's assertion, Dr. Hutfless did not "categorically dismiss" the clinical trials but rather she spent seven pages in her report detailing why the clinical trials did not provide support for an absence of a causal relationship. (*See* Hutfless Report, Ex. 1, at 28-35). Her review found that the clinical trials were not designed to assess OIE or powered to assess causality. (*Id.* at 23-24, 28-35.) Daiichi's epidemiologist Dr. Risch relied on her analysis and concluded the same. (Risch Dep. Tr., Ex. 25, at 122:4-22.) Hutfless's calculations revealed that the ROADMAP study was not sufficiently powered to detect any of the relative differences of celiac disease[10] given the background rate of gastrointestinal problems in the diabetic population studied. Dr. Risch agreed with this conclusion. (*Id.*) Dr. Hutfless's conclusion is consistent

[10] Dr. Hutfless selected the incidence rate of celiac disease because the Mayo Clinic case series (Rubio Tapia 2012 study at Ex. 26) and the FDA request for more information were based on the identified association between olmesartan and celiac-like symptoms. (*See* Hutfless Report, Ex. 1, at 29).

with the letter to the editor authored by the ROADMAP investigators, Menne and Haller, who concluded "[w]e cannot rule out" the causal relationship based on ROADMAP. (*See* Report, Ex. 1, at 31; Menne study, Ex. 27.)

3. Dr. Hutfless Describes A Plausible Biological Mechanism Supported by the Medical Literature.

To evaluate biological plausibility, Dr. Hutfless examined the literature to identify articles that described a biologically plausible mechanism by which olmesartan causes enteropathy. (*See* Report, Ex. 1, at 9-10; Dep. Tr., Ex. 2, at 197:3-10). Dr. Hutfless identified a number of articles in the peer-reviewed literature, including *Marietta* which found evidence of immune reaction – i.e., increased IL-15 and CD8+T cells – in duodenal biopsies of patients suffering from OAE. *See* Marietta, at Ex. 11; *see also* Hutfless Dep. Tr., Ex. 2, at. 391:1-11; 398:3-19. The purpose of this study was to "determine the mechanism in olmesartan-associated enteropathy." *Marietta* at 2. Dr. Hutfless also found a study by de Araujo of rats exposed to olmesartan that experienced enteropathy and malabsorption. (*See* Hutfless Report, Ex. 1, at 9; Hutfless Dep. Tr., Ex. 2, at 381:4-16.)

There is no requirement that mechanism be absolutely proven. A biological plausibility opinion is admissible as long as it is coherent with existing knowledge. *In re Zicam Cold Remedy Mktg. Sales Prac. & Prods. Liab. Litig.*, 2011 U.S. Dist. LEXIS 20356, *110-112 (D. Ariz. Feb. 24, 2011). Thus, "the fact that an expert does not use absolute terms but rather couches the opinion in terms of 'can' or 'may'

does not render it speculative or unreliable." *In re Trasylol Prods. Liab. Litig.*, 2010 U.S. Dist. LEXIS 52408, *150-51 (S.D. Fla. Mar. 19, 2010). Surely, Dr. Hutfless's stated mechanism meets this test as the Marietta paper demonstrates, "the mechanistic pathways present in OAE pathogenesis are similar to those of innate immune responses to gliadin in coeliac disease." *Marietta* at 9. Indeed, this Bradford-Hill criteria may be satisfied by less rigorous evidence than provided by Marietta. *Reference Manual* at 605 ("hypotheses are sometimes accepted under this factor."). Moreover, her reliance on de Araujo is proper as animal studies can "provide useful data about humans," are "not per se inadmissible, rather "should be subjected to substantive analysis, just like other scientific evidence." *Metabolife Int'l, Inc. v. Wornick*, 264 F.3d 832, 842 (9th Cir. 2001); *In re Trasylol Prods. Liab. Lit.*, 2010 U.S. Dist. LEXIS 52408, *152 (S.D. Fla.); *see also Hopkins v. Dow Corning, Corp.*, 33 F.3d 1116, 1125 (9th Cir. 1994) ("corroborating evidence found in studies conducted on animals" admissible); see also *In re Neurontin*, 612 F. Supp. 2d at 127 (allowing use of peer-reviewed animal studies); *In re Silicone Gel Breasts Implants Prods. Liab. Litig.*, 318 F. Supp. 2d 879, 910-911 (C.D. Cal. 2004) (noting reliance by researchers and agencies on relevant animal studies); *Ruff v. Ensign-Bickford Indus., Inc.*, 168 F. Supp. 2d 1271, 1281 (D. Utah 2001) (affirming animal studies as sufficient basis for opinion on general causation). The fact that another paper by de Araujo suggests an alternative finding, as Daiichi claims, does not

undermine this reliance. It simply goes to the weight of Dr. Hutfless's assessment of de Araujo and not her reliance upon it. *Glynn*, 2013 WL 1558690, at *2.

4. Dr. Hutfless Properly Considered Whether Other ARBs May Be Associated With SLE.

Dr. Hutfless did not "dismiss" the potential association of other ARBs and enteropathy, but rather used the case reports, case series, FAERS data, epidemiological studies, and the FDA's statements and analysis, for the very purpose of examining SLE with olmesartan and the risk with other ARBs, which all factored into her specificity analysis. (*See* Hutfless Report, Ex. 1, at 8-9; Hutfless Dep. Tr., Ex. 2, at 407:7-408:1; 439:13-440:15.) In contrast, Daiichi's epidemiologist Dr. Hansen did not compare reporting rates of olmesartan to the other ARBS, because "Dr. Hutfless had graciously done that before." (Hansen Dep. Tr., Ex. 5, at 246:7-247:9.) The only criticism by Dr. Hansen was her "judgment call" of using a narrow set of preferred terms. (*Id.*) The focus of the reliability inquiry is on the expert's principles and methodology, not on her conclusions. *Glynn v. Merck Sharp & Dohme Corp.*, 2013 WL 1558690, at *2. Likewise, Daiichi's other epidemiologist, Dr. Risch, never performed a disproportionality analysis of the FAERS database. (*See* Risch Dep. Tr., Ex. 25, at 117:16-22.)

Daiichi's only criticism is that Dr. Hutfless did not perform a class-wide analysis on all ARBs and enteropathy, claiming that "***If*** such evidence exists, it argues against specificity." (*See* Defs. Br. at 38-39.) Such evidence simply does

not exist according to both the medical literature and the FDA's analysis. *See* FDA Track Safety Issue (TSI) Memorandum, at Ex. 18 ("the other ARBs do not appear to demonstrate evidence for an ARB-induced sprue-like enteropathy"); 7/3/13 Drug Safety Communication to Healthcare Providers and Patients, Ex. 4 ("Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan"). Daiichi cannot possibly argue Dr. Hutfless's methodology is unreliable based on entirely nonexistent evidence. Instead, Dr. Hutfless correctly considered all the evidence that *does* exist when examining the Bradford Hill factor for specificity.

5. Dr. Hutfless Properly Relied Upon 60 MedWatch Cases Submitted by Daiichi to the FDA.

Dr. Hutfless includes in her Bradford-Hill analysis of general causation, 60 MedWatch cases reported by Daiichi to the FDA. These reports describe patients experiencing symptoms of diarrhea, vomiting or celiac disease while on olmesartan, and each involves a serious outcome and evidence of positive rechallenge. (*See* Hutfless Report, Ex. 1 at 6-7) (including MedWatch cases in Bradford Hill analysis). These 60 cases were all independently reviewed by plaintiffs' gastroenterologist expert, Dr. Leffler, who "considered the different causes of enteropathy, made a differential, ruled out other plausible alternatives, and determined they were indeed

caused by olmesartan enteropathy." (Leffler Dep. Tr., Ex. 28, 200:17-21.)[11] With input from Dr. Leffler, Dr. Hutfless also considered the 60 cases under the WHO-Uppsala Monitoring Centre causality assessment system—a well-accepted tool used by Daiichi—and concluded that 90% of the cases were "certain" or "probable/likely" related to olmesartan use. (*See* Hutfless Report, Ex. 1, at 17.)

Daiichi does not challenge—nor could it—the substance of the 60 MedWatch cases. Instead, Daiichi makes a convoluted attack on how the 60 MedWatch cases were selected from among thousands of gastrointestinal adverse events, falsely accusing the plaintiffs' experts of giving differing accounts of the selection and claiming the methodology was hidden. Daiichi faults Dr. Hutfless for seeking input from a clinician experienced in olmesartan enteropathy, although epidemiologists regularly consult with physicians in making causal conclusions. *See e.g., Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd., 286 F.R.D. 266, 271 (W.D. Pa. 2012)* ("It is well-settled that one expert may rely upon another expert's opinion in formulating his own."); *In re Jacoby Airplane Crash Litig.,* 2007 U.S. Dist. LEXIS 69291, at *52 (D.N.J. Sep. 18, 2007) ("It is common in technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert knowledge not possessed by the first expert").

[11] As part of that review, Dr. Leffler looked not only at the MedWatch forms but the source files—or background information—compiled by Daiichi for each case. (*See* Leffler Dep. Tr., Ex. 28, at 201:4-7.)

Finally, Daiichi claims Dr. Hutfless failed to consider "alternative causes" in making her WHO causal assessments, because she chose not to use information derived from Naranjo Question No. 5—which asks "[a]re there alternative causes (other than the drug) that could on their own have caused the reaction." Drs. Leffler and Hutfless agreed this Naranjo inquiry was too nonspecific for assessing common adverse events, like diarrhea, that can potentially have many causes. (Hutfless Dep. Tr., Ex. 2, at 130:18-133:5; *see also* Hutfless Report, Ex. 1, at 17.) Thus, to make the analysis more thorough and specific to olmesartan enteropathy, Dr. Hutfless relied on answers that Dr. Leffler provided to three questions: is there (1) an underlying medical condition/comorbidity, (2) other medication, or (3) allergy that could have caused the adverse event. (*Id.*; *see also* Hutfless Dep Tr., Ex. 2, at 133:19-134:1.) Thus, Daiichi essentially faults plaintiffs' experts for adopting a more rigorous "alternative cause" analysis.

a. The 60 MedWatch Cases Provide Reliable Evidence of General Causation.

Daiichi's experts completely ignore these critical 60 MedWatch cases of positive dechallenge and rechallenge. But the FDA and peer-reviewed literature have not. The FDA recognized this dechallenge/rechallenge phenomenon when requiring a warning (*see* 7/3/2013 FDA Drug Safety Communication, Ex. 4, at 3) as did countless other scientists publishing in the peer-reviewed medical literature (*see* Hutfless Report, Updated Table 10, Ex. 3) (198 positive dechallenge cases and 22

positive rechallenge cases identified in the medical literature). These reports have a powerful role in a causal assessment. The medical textbooks and literature are replete with references to the importance of dechallenge and rechallenge. Strom's *Pharmacoepidemiology* textbook states "[c]ase reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment." Strom BL, Chapter 3, *Basic Principles of Clinical Epidemiology Relevant to Pharmacoepidemiologic Studies*, in Strom BL, Pharmacoepidemiology 86 (5th ed. 2012), at Ex. 29. Similarly, it has been stated that "[a] well-document positive rechallenge, intentional or incidental, may irrefutably prove the connection between a drug and an adverse reaction." Meyboom et al, *Causal or Casual? The Role of Causality Assessment in pharmacovigilance*, Drug Safety 1997 Dec; 17(6): 374-389 at 383, at Ex. 30.

The *Reference Manual on Scientific Evidence* states "when such data are available and eliminating exposure reduced the incidence of disease, this factor strongly supports a causal relationship." *Id*. at 605. Thus, courts have repeatedly deemed dechallenge/rechallenge data "particularly useful in determining whether a causal relationship exists." *Rider v. Sandoz Pharmaceuticals Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002). "Rechallenge and dechallenge data is substantially more

valuable than run-of-the-mill case reports because a patient's reactions are measured against his prior reactions." *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001). Indeed, "[a] positive rechallenge, at least in the absence of clear evidence to the contrary, is generally considered as the strongest and most conclusive evidence that the drug is the cause of the adverse reaction." *Rolland v. Smithkline Beckman Corp.*, 1990 U.S. Dist. LEXIS 6252, at *109-10 (E.D. Pa. May 22, 1990); *Eve v. Sandoz Pharm. Corp.*, 2001 U.S. Dist. LEXIS 4531, at *65, n. 15 (S.D. Ind. Mar. 7, 2001) ("evidence of positive dechallenge and rechallenge, on its own, may suffice to establish causation").

b. Dr. Hutfless Correctly Selected the 60 MedWatch Cases.

Daiichi claims that Dr. Hutfless could not explain the methodology by which the 60 MedWatch cases were selected. (Def. Br. at 2.) That is simply not true. The methodology was clear. The 60 MedWatch cases were selected because they described diarrhea, vomiting or celiac disease symptoms, that were serious and reappeared on rechallenge. (*See* Hutfless Rpt., Ex. 1 at 17; Hutfless Dep. Tr., Ex. 2, at 67:17-68:4; 105:12-106:5; 175:17-176:2.) Daiichi's motion does not contest whether any of the 60 MedWatch cases meet this criteria. Thus, the methodology for selecting the 60 cases was necessarily sound as it produced cases that exactly matched criteria.

There is no "mystery" surrounding how these criteria were developed. Dr. Kessler developed the criteria based on his review of the literature and then asked for feedback from Dr. Leffler. (*See* Kessler Dep. Tr., Ex. 31, at 197:7–198:1.) Dr. Leffler "confirmed that the symptoms in the selection criteria overall were appropriate to identify cases of olmesartan enteropathy." (*See* Leffler Dep.. Tr., Ex. 27, at 353:12-17.) This was also understood by Dr. Hutfless. (*See* Hutfless Dep. Tr., Ex. 2, at 65:7-66:2.) Nor is there any dispute these were appropriate criteria for assessing general causation. Daiichi uses similar criteria to identify cases, citing "nausea, vomiting and diarrhea and signs typical of olmesartan induced sprue-like enteropathy such as weight loss." (*See* Tina Ho Dep. Tr., Ex. 12, at 451:18-453:15.)

That Drs. Hutfless and Leffler reviewed a larger set of 335 MedWatch cases before relying on the 60 MedWatch rechallenge cases is a red herring. Daiichi does not dispute the authenticity of any of these 335 MedWatch cases. They simply represent more reports of gastrointestinal symptoms while on olmesartan. (*See* Hutfless Dep. Tr., Ex. 2, at 63:1-23, 64:1-6.)

There is also no mystery concerning the methodology by which the 335 MedWatch cases were compiled. Dr. Hutfless initially requested MedWatch cases that contained "relevant symptoms" of enteropathy associated with olmesartan based on input from Dr. Leffler and her review of the olmesartan literature. (*See* Hutfless Depo. Tr., Ex. 2, at 53:10-17.) Dr. Hutfless also requested that the MedWatch cases

include evidence of positive dechallenge. (*Id.* at 55:3-9.) As a result, 335 MedWatch forms were provided to Dr. Hutfless. (*Id.* at 107:32-108:2.) As described in both Dr. Hutfless and Dr. Leffler's depositions, Dr. Leffler and two gastroenterologists working under his direction, extracted information from the each of 335 MedWatch forms that was placed in a "single database" for Dr. Hutfless's further analysis. (*See* Leffler Dep. Tr., Ex. 28, at 326:15-327:15; Hutfless Dep. Tr., Ex. 2, at 70:23-71:21.) In addition, Dr. Leffler and his team evaluated whether other medical conditions/co-morbidities, medications or allergies could have contributed to the GI adverse events and answered a series of questions from the Naranjo causality assessment tool, including questions pertaining to dechallenge and rechallenge (questions 2, 3, 4). (*Ssee* Leffler Dep. Tr., Ex. 28, at 325:23-326:3.) All information that Dr. Leffler and his team extracted from the 335 MedWatch forms was provided to Daiichi's counsel prior to Dr. Leffler's deposition and again before Dr. Hutfless's deposition. (*See* Ex. 32, Plaintiffs' Cover Letter Producing Documents in Response to Deposition Notice)).[12]

Thus, this was not a "poorly defined process" of selecting the MedWatch cases and is certainly not a proper basis for exclusion. *Ruiz-Troche v. Pepsi Cola*,

[12] Daiichi's insinuation this information was produced "after Dr. Hutfless's Deposition" is simply untrue. (Defs. Br. at 25.) The documents were provided prior to Dr. Hutfless's deposition (*see* Plaintiffs' Cover Letter Producing Documents Responsive to Drs. Hutfless and Leffler's Deposition Notices, Ex. 32).

161 F.3d 77, 85 (1st Cir. 1998) (citing *Daubert*, 509 U.S. at 590) ("In short, *Daubert* neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance. It demands only that the proponent of the evidence show that the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.").

c. Dr. Hutfless's Methodology For Assessing The MedWatch Cases Is Valid And Consistent.

Dr. Hutfless determined the 60 MedWatch cases contributed to a number of Bradford-Hill considerations, including temporality (all cases had positive dechallenge/rechallenge), consistency (all cases were "similar to those reported in the literature"), specificity (adverse events were specific to olmesartan as alternative causes were excluded) and experiment (all cases had a positive rechallenge). (*See* Hutfless Report, Ex. 1, at 18-19.) Daiichi's motion does not challenge this Bradford-Hill analysis, instead Daiichi focuses on her determination that 90% of the complete published case reports were "certain" or "probable/likely" related to olmesartan under the WHO scale.

There is widespread agreement that WHO is an appropriate methodology for assessing causality. The peer reviewed literature employs the WHO method, including a study recently published by FDA physicians using the criteria to assess, among other things, olmesartan and sprue like enteropathy. Pierce et al., *Evaluation of Facebook and Twitter Monitoring to Detect Safety Signals for Medical Products:*

An Analysis of Recent FDA Safety Alerts, Drug Safety (2017) 40:317-331, at Ex. 33. Dr. Hutfless was certainly qualified to use it, as she has authored an article in the peer reviewed literature where adverse events were assessed under WHO and Naranjo. Selvaraj et al., *Use of Case Reports and the Adverse Event Reporting System in Systematic Reviews: Overcoming Barriers to Assess the Link Between Crohn's Disease Medications and Hepatosplenic T-cell Lymphoma,* Systematic Reviews 2013, 2:53, at Ex. 34.

Defendants' claim causality assessment tools like WHO and Naranjo cannot be used in considering general causation. (Defs. Br. at 17), but Daiichi's own expert, Dr. Risch, spent nearly half of his expert report on general causation applying the WHO and Naranjo criteria to published case reports and case series. (*See* Risch Report, Ex. 35, at 17-19.)

It was standard operating procedure at Daiichi to use WHO in making causal assessments of adverse events. (*See* Kessler Report, Ex. 36, at 13-14,). In fact, Daiichi's SOP provided that an adverse event was to be causally assessed "definitely related" if the following three criteria were met:

> [1] Follows a reasonable temporal sequence from study product administration.
> [2] Abates upon discontinuation of the study product (dechallenge).
> [3] Is confirmed by reappearance of the reaction on repeat exposure (rechallenge).

(*Id.*) Notably, Daiichi's causal assessment of "definitely related" did not even require consideration of "alternative causes," such as underlying medical conditions or concomitant medications. Using Daiichi's SOP, all 60 MedWatch cases considered by Drs. Hutfless and Leffler would have been scored "definitely related" to olmesartan. As Dr. Kessler—former FDA Commissioner—testified "if I were sitting there at DSI [referring to Daiichi], using that causality assessment in 2007, the emphasis on dechallenge and positive rechallenge was the basis for DSI concluding that there was a definite causality." (*See* Kessler Dep. Tr., Ex. 31, at 202:19-23.)

But, as the expert report and testimony make clear, Dr. Hutfless used a more conservative approach than that embraced internally by Daiichi. Dr. Hutfless included consideration of "concomitant comorbidities, medications or allergies," (Hutfless Report, Ex. 1, at 17), thus concluding that 24 of the 60 cases were "certain," 30 were "probable," and six were "possible." (*Id.*; *see also* Table 4 from Figures, Ex. 1.) Dr. Hutfless's conclusions are supported by Dr. Leffler's differential diagnoses that all 60 MedWatch forms included in Dr. Hutfless's report were "cases of olmesartan-induced enteropathy." (*See* Leffler Dep. Tr., Ex. 28, at 200:11-13; 206: l. 4-11.)

Daiichi patronizingly claims that Dr. Hutfless placed "unblinking reliance" on Dr. Leffler. (Defs Br. at 20.) The method by which Dr. Hutfless worked with

Dr. Leffler does not deviate from research methods she uses outside the courtroom. As Dr. Hutfless testified, "the way that I conduct my science is I work collaboratively with a clinician to understand their perspective, since I don't have an M.D." (*See* Hutfless Dep. Tr., Ex. 2, at 98:3-7.) Here, she spoke many times with Dr. Leffler including "about the symptoms that were relevant to olmesartan-induced enteropathy and worked with him to identify a specific list of cases from the MedWatch that I could rely upon as a clinician determining that those cases had olmesartan-induced enteropathy." (*Id.* at 98:9-17.) Relying on the input of other experts only enhances the reliability of Dr. Hutfless's opinions. *See In re Phenylpropanolamine Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1248 (W.D. Wash. 2003) (expert's reliance on case reports, textbooks and treatises, and "clinical experience of several experts" satisfies *Daubert*).

Dr. Hutfless also cross-checked Dr. Leffler's conclusions from the MedWatch cases against Daiichi's own internal determinations (Hutfless Dep. Tr., Ex. 2, at 117:21-118:17) and independently confirmed that Dr. Leffler had accurately extracted information from the MedWatch form (*id.* at 113:11-17). Thus, the record in no way supports Daiichi's claim that Dr. Hutfless "failed to assess the validity" of Dr. Leffler's work. (Defs. Br. at 20.)

Nor should there be any controversy about Dr. Hutfless's ultimate decision to rely upon the WHO rather than Naranjo. While both are validated scales for

assessing causality, the Naranjo scale has been criticized because of the variability introduced by question number 5—alternative causes. *See e.g.* Naranjo, et al., *A method for estimating the probability of adverse drug reactions*, Clin Pharmacol Ther 1981 Aug;30(2):239-45, at Ex. 38 (Naranjo himself stating "[t]he assessment of question 5 (alternative causes) led to the most disagreement"); Rehan, *Causality Assessment of Spontaneously Reported Adverse Drug Events: Comparison of WHO-UMC Criteria and Naranjo Probability Scale*; International Journal of Risk & Safety in Medicine 2007, 1, Ex. 38, at 3-4 (preferring WHO over Naranjo), at Ex. 39. Even Daiichi's expert agreed not all Naranjo questions applied in this case. (*See* Risch Report, Ex. 35, at 29) ("some of the Naranjo characteristics can be argued not to be applicable to the relationship under current discussion"). Here, Dr. Hutfless and Dr. Leffler agreed question number 5 was too nonspecific to properly assess alternative causation and instead required Dr. Leffler to answer a series of specific questions on alternative cause, *i.e.,* was the adverse event caused by a medical condition, other medications or an allergy. (*See* Hutfless Dep. Tr., Ex. 2, at 130:9-133:5.)

Dr. Hutfless did not—as Daiichi argues—"assume" there was no alternative cause when information was missing from the MedWatch forms (Defs. Br. at 3.) Dr. Hutfless specifically discussed with Dr. Leffler, for each of the 60 MedWatch forms where "not mentioned" was coded by his team, whether any alternative cause

might have played a role in the GI adverse event reported (Hutfless Dep. Tr., Ex. 2, at 430:19-431:5; 431:22-432:5.) Dr. Hutfless testified that "using the assessments that he made based on reviewing the criteria in the MedWatch forms as well as the source files," Dr. Leffler "instructed me that when it said 'not mentioned,' that meant no." (Hutfless Dep. Tr., Ex. 2, at 430:21-431:5; *see also* 431:22-432:5 ("[T]he conversation that I had with Dr. Leffler was that 'not mentioned' was equivalent to no contribution of each of these categories.")).

d. Dr. Hutfless Did Not Err In The WHO Causal Assessment Of Eight Specific MedWatch Cases.

Daiichi, ignoring the vast majority of the MedWatch forms Dr. Hutfless relies upon, centers its criticism on eight cases[13] occurring between 2004 and 2006. That criticism is undeserved as the evidence reflects that Dr. Hutfless properly considered alternatives (Daiichi's principle complaint is that she did not) and, in most instances, Dr. Hutfless's causal assessment was in agreement with, or more conservative than, Daiichi's. In addition, alternative causes were eliminated through the confirmation of positive rechallenges. (*See* Leffler Dep. Tr., Ex. 28, at 226:17-20.) Specifically:

[13] Nowhere in Dr. Hutfless's report or deposition does she claim to rest her general causation opinion "on a review of eight MedWatch reports." (*See* Defs. Br. at 13.) As already explained, her general causation opinions were formed by applying the Bradford Hill criteria to multiple lines of evidence, including published peer-reviewed medical literature and case reports, epidemiological studies, conducting a FAERS analysis, clinical trials, *and* reviewing sixty MedWatch cases reported by Daiichi to the FDA. (*See* Hutfless Report, Ex. 1, at 35; Hutfless Dep. Tr., Ex. 2, at 290:18 – 292:6.)

- **SU-2004-002638** describes a patient who "experienced 'rampant diarrhea.'" (*See* OLM-DSI-000001197522). Daiichi coded this case as including two positive rechallenges (*id.*) Daiichi's SOP would require a WHO score of "definitely related" (*see* OLM-DSI-0007160734, Ex. 40 at 749,); Dr. Hutfless's WHO assessment was "probable" (*see* Hutfless Report, Ex. 1, at 18.) Daiichi speculates that Dr. Leffler concluded the patient's giardia diagnosis was an alternative cause that required a lower WHO score than "probable." (Defs. Br. at 25.) This is a mischaracterization as Dr. Leffler testified he ruled out other plausible alternatives. (*See* Leffler Dep. Tr., Ex. 28, at 200:17-21) and his notes confirm he considered giardia (*see id.* at 200:17-21) and his notes confirm he considered giardia (*see* Leffler Dep. Ex. 24, attached as Ex. 37).

- **SU-2005-004027** describes a patient with vomiting and dehydration so severe two hospitalizations were required. (*See* OLM-DSI-000001096783, Ex. 40.) Daiichi determined the patient experienced a positive dechallenge/rechallenge (*id.*), thus requiring Daiichi under its SOP to conclude the case was "definitely related" to olmesartan whereas Dr. Hutfless's assessment was "probable/likely." (Hutfless Dep. Tr., Ex 14, at 44.) Daiichi claims this patient's misdiagnosis of celiac disease was an "alternative cause" requiring Dr. Hutfless to find causality not probable/likely under WHO. But Dr. Leffler made no such conclusion, performing a differential diagnosis that ruled out alternative causes. (Leffler Dep. Tr., Ex. 28, at 200:17-21) and confirmed the patient's dehydration requiring hospitalization was caused by olmesartan, not another medicine or medical condition. (*Id.* at 231:9-236:11.)

- **SP-2006-003299** describes a patient who experienced vomiting, diarrhea and weight loss requiring multiple hospitalizations. (*See* OLM-DSI-0001099889-R, Ex. 40.) Daiichi asserts that Dr. Hutfless could not have assessed causality under WHO as "certain" because the MedWatch form makes no mention of other medications the patient might have been taking. (Defs. Br. at 25.) This claim is specious as Daiichi concluded the same—that the causal relationship between olmesartan and the event was "'definite' due to the positive rechallenge." (*See* OLM-DSI-00001096783, Ex. 40.) When an expert's opinion matches that of the defendants, "proper fit" under *Daubert* is demonstrated. *In re Mentor Corp. Obtape Transobturator Sling Prod. Liab. Litig.*, 2010 U.S. Dist. LEXIS 42237, *11-12 (M.D. Ga. 2010).

- **SU-2006-003369** is a ROADMAP study clinical patient hospitalized multiple times due to "gastroenteritis" (*see* OLM-DSI-0004767148-R, Ex 40.)

Dr. Hutfless's WHO assessment was "probable/likely." (*See* Hutfless Dep. Tr., Ex. 44, at 13, attached as Ex. 42.) Daiichi claims Dr. Hutfless's WHO causal assessment of "probable/likely" is suspect but Daiichi reached an identical conclusion. In 2007, Daiichi assessed "the causal relationship between [olmesartan] and gastroenteritis . . . as probable," upgrading it in 2009 to "related." OLM-DSI-0004767148-R at 150, 151. Daiichi's claim that Dr. Leffler considered this case to include an alternative cause because of his Naranjo scoring is unfounded. (Defs. Br. at 25.) Dr. Leffler describes this case at length in his report as enteropathy caused by olmesartan. (*See* Leffler Report, Ex. 42, at 16.)

- **SU-2006-005001** is a patient who experienced "vomiting, diarrhea, fever and chills" requiring multiple hospitalizations**.** (OLM-DSI-0004774010-R, Ex. 40.) Daiichi claims this patient's "celiac disease" misdiagnosis should make Dr. Hutfless's WHO assessment "probable/likely." (Defs. Br. at 25.) But in 2012, Daiichi informed FDA it did not consider the "celiac disease diagnosis," for this patient as either a "strong" or "potential" confounding cause of the injuries. (*See* OLM-DSI-0001247542 at 602, Ex. 40.)

- **SU-2006-005321** "experienced severe diarrhea and hypotension" requiring hospitalization" and experienced a reoccurrence when olmesartan was restarted. OLM-DSI-0004774046-R. Thus under its SOP, Daiichi considered this case "definitely related" to olmesartan. *Id.* Dr. Hutfless's WHO assessment was also "certain." (Hutfless Dep. Tr., Ex. 44 to deposition, attached hereto as Ex. 42, at 3.) Daiichi claims Dr. Hutfless should have reached a different determination because there was no information reported about past medical history or other medications, but—as Dr. Leffler testified—medical history is "secondary to the diagnoses" of olmesartan induced enteropathy when—as here—there is clear evidence of positive rechallenge. (Leffler Dep. Tr., Ex. 28, at 229:19-21; *see also* 227:14-228:2) (alternative causes unlikely when patient experiences diarrhea symptoms with each re-exposure to olmesartan).

- **SU-2007-005527** experienced vomiting and diarrhea, with 30 pound weight loss and three hospitalizations. Daiichi insinuates Dr. Hutfless included a case where the diarrhea continued after discontinuing olmesartan, *i.e.,* a negative dechallenge/rechallenge case. Daiichi Brief, p. 26. Again this is false—in 2012 Daiichi informed the FDA that this case involved two positive rechallenges. (*See* OLM-DSI-00099888_R at 93, Ex. 40.) Thus, Dr. Hutfless's score of "probable/likely" caused by olmesartan is entirely consistent with Daiichi's.

- **SU-2006-005596** experienced a 70-pound weight loss and multiple hospitalizations for diarrhea and other symptoms, dehydration and anemia. (*See* OLM-DSI-0001099361_R, Ex. 40.) Daiichi claims a diagnosis of celiac disease in this patient meant Dr. Hutfless could not have concluded, under WHO, that the causal association was "probable/likely." But Daiichi did not identify "celiac disease" as an alternative cause when describing this case to the FDA. (OLM-DSI-00014774010, Ex. 40.) Instead, Daiichi noted that the patient only recovered when he—on two separate occasions—was taken off olmesartan. (*Id.*) Nor did Dr. Leffler consider "celiac disease" as an alternative cause. Dr. Leffler "ruled out other plausible alternatives." (Leffler Dep. Tr., Ex. 28, at 200:17-21) for this case (*see* Hutfless Dep. Tr., Ex. 2, at 430:21-431:5; *see also* 431:22-432:5).

e. Dr. Hutfless's WHO Causal Assessment Of The Published, Peer-Reviewed Literature Was Reliable.

Daiichi is critical of Dr. Hutfless's WHO casual assessment of the published case reports. (Defs. Br. at 27.) Based on her finding that 198 cases (93% of all published cases) reported a positive dechallenge and 22 cases (10%) reported a positive rechallenge, Dr. Hutfless concluded that "majority of the cases" could be assessed "probable" under WHO. (*See* Ex. 1 at 22; Ex. 3.)

Daiichi's expert did a similar causal scoring of the literature, finding that most literature fell into the "possible-probable" category. (*See* Risch Report, Ex. 35, at 26.) Moreover, Dr. Hutfless's conclusion that the case reports and case series support causality finds ample support in the literature. *See e.g.*, *Relapsing Olmesartan-Associated Ileitis,* Ann Pharmacother., 2016 Dec; 50(12): 1070, at Ex. 43 ("definite **causal** role for olmesartan"); *Clinical, Laboratory, Serological, and Histological Profile of Sprue-Like Enteropathy Associated with Olmesartan Use*,

Rev. Esp. Enferm Dig. 2016 Oct; 108(10):68505, at Ex. 44 ("olmesartan must be considered as a **cause** of severe diarrhea"); *Olmesartan-Associated Enteropathy: Results of a National Survey*, Aliment Pharmacol. Ther. 2014; 40(9): 1103-9, at Ex. 45 ("Olmesartan **causes** a severe and immune-mediated enteropathy, with or without villous atrophy") (emphases added).

The fact that numerous peer-reviewed publications have concluded—like Dr. Hutfless—that olmesartan is causing enteropathy establishes that Dr. Hutfless's opinion relies upon "good grounds" and is supported by "appropriate validation." *Daubert* 509 U.S. at 590; *cf. McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1239 (11th Cir. 2005) (holding that "[t]he court need not undertake an extensive Daubert analysis . . . when the medical community recognizes the agent causes the type of harm a plaintiff alleges").

CONCLUSION

For the foregoing reasons, Daiichi's motion to preclude Dr. Hutfless's opinions under *Daubert* should be denied. Dr. Hutfless applied a valid methodology, relying primarily on an independent systematic literature review and properly applying the Bradford Hill criteria. Whatever criticisms the defense may have are directed to Dr. Hutfless's conclusions, which are fully consistent with the consensus in the peer reviewed literature, can be explored on cross-examination at trial.

Respectfully submitted,

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Dated: April 21, 2017

CERTIFICATE OF SERVICE

I hereby certify that on April 21, 2017, the attached Plaintiffs' Memorandum of Law In Opposition to Defendants' Brief In Support of Motion to Exclude Testimony of Susan Hutfless, Ph.D., as well as supporting documents, were filed with the Clerk of the U.S. District Court, Camden Division, Camden, New Jersey and all counsel of record were served *via* the ECF filing system.

In addition, a courtesy copy will be sent *via* Federal Express to:

Hon. Robert B. Kugler, U.S.D.J.
United States District Court for the District of New Jersey
Mitchell H. Cohen Building & U.S. Courthouse
4th & Cooper Street, Courtroom 4D
Camden, New Jersey 08101

Hon. Joel Schneider, U.S.M.J.
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